Biosimilars, Biobetters, and Beyond

April 2017

Objectives

• Discuss the current status of regulatory and legal decisions and their anticipated impact on biosimilar availability
• Explain the critical elements of biosimilar approval based upon the products that have been licensed to date
• Describe the economic model that is beginning to take shape in the U.S. biosimilars market
• Review the impact of new drug development on the anticipated uptake of biosimilars
It's Been a Busy Couple of Months!

November 2016
• Launch of Inflectra

December 2016
• Finalization of clinical pharmacology and naming guidances

January 2017
• Supreme Court agrees to hear Amgen vs. Sandoz
• Interchangeability guidance published
• Trastuzumab and adalimumab biosimilar applications accepted

February 2017
• Acceptance of biosimilar application for pegfilgrastim
• New lawsuit – Genentech vs. Amgen

And Then There Were Four (Approved Biosimilars)

First biosimilar - Filgrastim-sndz (Zarxio; Sandoz)
• Approved March 6, 2015; launched September 3, 2015

Second biosimilar - Infliximab–dyyb (Inflectra; Celltrion/Pfizer)
• Approved April 5, 2016; launched November 2016

Third biosimilar – etanercept-szzs (Erelzi; Sandoz)
• Approved August 30, 2016; estimated launch date: ??????

Fourth biosimilar – adalimumab-atto (Amjevita; Amgen)
• Approved September 23, 2016; estimated launch date: ??????

PDUFA = Prescription Drug User Fee Act
The Pink Sheet, FDA Performance Tracker, Pending Biosimilars (subscription), accessed January 20, 2017;
Drugs@FDA, accessed October 5, 2016
Biosimilar Pipeline: 7 in 2017?

<table>
<thead>
<tr>
<th>INN</th>
<th>Manufacturer</th>
<th>Application Submitted</th>
<th>Estimated FDA Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab (SB2)</td>
<td>Samsung Bioepsis</td>
<td>3/2016</td>
<td>4/2017</td>
</tr>
<tr>
<td>Pegfilgrastim (CHS-1701)</td>
<td>Coherus</td>
<td>8/2016</td>
<td>6/2017</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Pfizer/Hospira</td>
<td>12/2016 (refiled)</td>
<td>6/2017</td>
</tr>
<tr>
<td>Trastuzumab (MYL-1401O)</td>
<td>Mylan and Biocon</td>
<td>11/2016</td>
<td>9/2017</td>
</tr>
<tr>
<td>Bevacizumab (ABP 215)</td>
<td>Amgen and Allergan</td>
<td>11/2016</td>
<td>9/2017</td>
</tr>
<tr>
<td>Adalimumab (BI 695501)</td>
<td>Boehringer Ingelheim</td>
<td>11/2016</td>
<td>9/2017</td>
</tr>
<tr>
<td>Pegfilgrastim (MYL-1401H)</td>
<td>Mylan and Biocon</td>
<td>12/2016</td>
<td>10/2017</td>
</tr>
</tbody>
</table>

The Pink Sheet, FDA Performance Tracker, Biosimilars, accessed 2/20/2017

Other Biosimilars Pending

- Sandoz (pegfilgrastim) and Apotex (filgrastim, pegfilgrastim) working on refiling previously submitted applications
- Ongoing litigation will determine the exact date of biosimilar launch

The Pink Sheet, FDA Performance Tracker, Biosimilars, accessed 2/20/2017
The Joy of Legal Issues and Debate

Ongoing Litigation

Issues
- patent dance (currently optional); 180 day notification (mandatory, post-approval)
- Supreme Court to hear Amgen vs. Sandoz, April 26th; decision late June/July

Other Cases
- Janssen vs. Celltrion (infliximab)
- Amgen vs. Apotex (pegfilgrastim)
- Amgen vs. Hospira (epoetin)
- Immunex vs. Sandoz (etanercept)
- Amgen vs. Sandoz (pegfilgrastim)
- AbbVie vs. Amgen (adalimumab)
- Genentech vs. Amgen (bevacizumab)

The Pink Sheet, February 17, 2017
Eleven Biosimilar Guidances Have Been Published

6 finalized
• Scientific considerations
• Quality considerations
• Questions and answers
• Formal meetings with FDA
• Clinical Pharmacology
• Non-proprietary naming

5 draft
• Reference product exclusivity
• Additional questions and answers
• Implementation of the “Deemed to be a License Provision”
• Biosimilar labeling
• Interchangeability

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065010.htm

What’s in a Name?

Two names for biologics
Core name = (e.g. infliximab)
Proper name = core name plus four letter suffix (e.g. infliximab-dyyb)
• Suffix must be unique and devoid of meaning
Will ultimately apply to all biologics

Why?
Prevent inadvertent substitution
Improve pharmacovigilance
Encourage use of FDA-designated suffixes
Advance accurate perceptions about biologicals

Naming in Practice

<table>
<thead>
<tr>
<th>Current</th>
<th>Proposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim</td>
<td>Filgrastim-jcwp</td>
</tr>
<tr>
<td>Filgrastim-sndz</td>
<td>Filgrastim-bflm</td>
</tr>
<tr>
<td>Tbo-filgrastim</td>
<td>Filgrastim-vkzt</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Epoetin alfa-cgkn</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Infliximab-hjmt</td>
</tr>
</tbody>
</table>

- Approved biosimilars with proper names per guidance: infliximab-dyyb, etanercept-szss, adalimumab-atto
- No timeline for implementation of proposed proper names for existing products


Interchangeability Guidance (FINALLY!)

**Key elements**
- Interchangeability requires switching study (or studies) and possibly post-marketing data
- Requirements affected by complexity of molecule, analytical characterization, and likelihood of immunogenicity adverse events (e.g. filgrastim vs. mAb)
- Cannot use non-US licensed data in switching study; in contrast to biosimilarity study

**60 day comment period**
- Submit comments at https://www.regulations.gov/

State Biosimilarity Legislation Continues

36 states have considered legislation
25 states, plus Puerto Rico have been signed into law

Common features
• FDA determination as interchangeable – “Purple Book”
• Physician dispense as written authority
• Physician notification, patient notification and consent of substitution
• Record keeping requirements
• Cost information to the patient


What Have We Learned from Biosimilars Approved to Date?
The ABC’s and E’s of Biosimilars

Accept the Accuracy of Analytics
Build a Bridge between biosimilar and non-US licensed originator biologic
Curb the expectation of clinical trials in every indication
   – Embrace extrapolation

Totality of the Evidence

Biosimilars Balancing Act

Clinical

Structural and Functional Characterization

Infliximab-dyyb Analytical Characterization

The Efficiency of Bridging

<table>
<thead>
<tr>
<th>Study (Dates)</th>
<th>Design (Objectives)</th>
<th>Patient Population (Total Number)</th>
<th>Treatment Arms</th>
<th>Number per arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT-P13 3.1 (Global, ex-US) 54 weeks (12/10 to 07/12)</td>
<td>R, DB, PG Comparative Clinical Study: Efficacy, Safety, PK, Immunogenicity</td>
<td>Moderate to Severe RA, MTX-IR N=606</td>
<td>CT-P13 3 mg/kg + MTX EU-approved infliximab</td>
<td>n = 302 n = 300</td>
</tr>
<tr>
<td>CT-P13 1.1 (Global, ex-US) 54 weeks (12/10 to 07/12)</td>
<td>R, DB, PG PK, Efficacy, Safety, Immunogenicity</td>
<td>Moderate to Severe AS N = 250</td>
<td>CT-P13 5 mg/kg EU-approved infliximab</td>
<td>n = 128 n = 122</td>
</tr>
<tr>
<td>CT-P13 1.4 Single Dose (10/13 to 02/14)</td>
<td>R, DB, PG, SD 3-way PK bridging: PK, Safety, Immunogenicity</td>
<td>Healthy volunteers N = 213</td>
<td>CT-P13 5 mg/kg EU-approved Remicade 5 mg/kg US-licensed Remicade 5 mg/kg</td>
<td>n = 71 n = 71 n = 71</td>
</tr>
</tbody>
</table>


What Is Extrapolation?

Extrapolation is:

- The use of data derived from a clinical study of a biosimilar in one indication to support the licensing of the biosimilar for other approved uses of the originator reference biologic
- A cornerstone of the biosimilarity principle
  - eliminates the need for redundant clinical trials
- Must be scientifically justified and is predicated on the level of understanding of many elements including:
  - the biologic's mechanism of action
  - pharmacokinetics and bio-distribution in different patient populations
  - immunogenicity and toxicity profiles in different patient groups
- Can vary in difficulty given the molecule in question

Science of Extrapolation

Originator

Indication #1

Indication #2

Indication #3

Biosimilar

Indication #1

Indication #2

Indication #3

Extrapolation is not from one clinical study of the biosimilar to other indications

Similarity between molecules allows extrapolation


Progression of Biosimilar Approvals

<table>
<thead>
<tr>
<th>Name</th>
<th>Zarxio</th>
<th>Inflectra</th>
<th>Erelzi</th>
<th>Amjevita</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Filgrastim-sndz (place holder) • Proposed name: filgrastim-bflm</td>
<td>Infliximab-dyyb</td>
<td>Etanercept-sz zs</td>
<td>Adalimumab-atto</td>
</tr>
<tr>
<td>Indications studied</td>
<td>Myelosuppressive chemotherapy</td>
<td>Rheumatoid arthritis • Ankylosing spondylitis</td>
<td>Plaque psoriasis</td>
<td>Rheumatoid arthritis • Plaque psoriasis</td>
</tr>
<tr>
<td>Indication coverage</td>
<td>All non-orphan indications</td>
<td>All non-orphan indications</td>
<td>All indications • However, no weight based dosing for children less than 63 kg (product only available in prefilled syringe)</td>
<td>All non-orphan indications</td>
</tr>
</tbody>
</table>

Summary of Approval Activities

- Four products approved to date
- FDA comfortable with extrapolation and bridging of data
- 2017 could bring the first instance of a second biosimilar for the same reference product and the first biosimilar for oncology indications
- Will have to monitor for impact of interchangeability guidance

Understanding Biosimilar Value and Other Impossible Tasks
The Dimensions of Payment (Medical and Pharmacy)

What’s Most Important? It depends…

**Inpatient**
- Acquisition price
- Distribution channel
- Market share incentive programs

**Outpatient infusion**
- Acquisition price
- Reimbursement
- Patient assistance programs

**Retail/Pharmacy Benefit Management**
- Acquisition price
- Manufacturer rebates
- Patient assistance programs
Medicare and Medicaid

Biosimilar Medicare Part B

- Biosimilar has unique Healthcare Common Procedure Coding System (HCPCS) code from originator
  - Filgrastim (biosimilar) = Q5101
  - Infliximab (biosimilar) = Q5102
- Biosimilars of the same originator share HCPCS codes
- Reimbursement =
  - 100% of biosimilar Average Sales Price (ASP) X 4.3% ASP of the originator
  - Must use two digit identifier to distinguish which biosimilar used
    - ZA = Novartis/Sandoz
    - ZB = Pfizer/Hospira

https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/Part-B-Biosimilar-Biological-Product-Payment.html

Medicare Part D and Medicaid

Medicare Part D

- Biosimilars currently not eligible for Coverage Gap Discount Program
- Biosimilars could cost more than originator in Part D

Medicaid rebate

- Biosimilar manufacturer rebate to be calculated according to the 23.1% level of sole sourced drugs

http://go.avalere.com/acton/attachment/12909/f-02c0/1/-/-/-/-/-/-/20160412_Patient%20OOP%20for%20Biosimilars%20in%20Part%20D.pdf; The Pink Sheet, January 3, 2017
What Savings Have We Seen?

**Filgrastim-sndz**
15% initial discount (WAC)

**Tbo-filgrastim**
19% discount (WAC)

**Infliximab-dyyb**
15% of originator infliximab WAC

WAC = wholesale acquisition cost


Elements of a Formulary Review Document (Biosimilar perspective)

- Brand and generic names and synonyms
- FDA approval information
- Pharmacology and mechanism of action
- FDA approved indications
- Potential non-FDA approved indications
- Dosage form and storage
- Recommended dosage regimens
- Pharmacokinetic considerations
- Use in special populations
- Pregnancy category and use during breast-feeding
- Comparisons of the drug's efficacy, safety, convenience, and costs with those of therapeutic alternatives
- Clinical trial analysis and critique
- Medication safety assessments and recommendations
  - Adverse drug reactions
  - Drug-drug, drug-food interactions
  - Sound-alike and look-alike issues
- Financial analysis

ASHP Guidelines on the Pharmacy and Therapeutics Committee and the Formulary System
Biobetters and Beyond

<table>
<thead>
<tr>
<th>Existing agent</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neulasta (pegfilgrastim)</td>
<td>• Pegfilgrastim auto injector (Neulasta® OnPro®)</td>
</tr>
<tr>
<td>Rituxan (rituximab)</td>
<td>• Rituximab subcutaneous</td>
</tr>
<tr>
<td>intravenous injection</td>
<td>• Obinutuzumab</td>
</tr>
<tr>
<td>Herceptin (trastuzumab)</td>
<td>• Pertuzumab</td>
</tr>
<tr>
<td></td>
<td>• Ado-trastuzumab emtansine</td>
</tr>
<tr>
<td>Remicade (infliximab)</td>
<td>• Guselkumab (IL-23 inhibitor for plaque psoriasis)</td>
</tr>
<tr>
<td>Humira (adalimumab)</td>
<td>• ABT-122 (bispecific antibody for TNF and IL-17)</td>
</tr>
<tr>
<td></td>
<td>• ABT-494 (Janus kinase-1 inhibitor)</td>
</tr>
<tr>
<td></td>
<td>• ALX-0061 (anti-interleukin-6 receptor) mAb</td>
</tr>
</tbody>
</table>

What Does This Mean to You?

- **Biosimilars have entered the market and more will be added in 2017**
- There still is a lack of understanding about these products
  - Relative safety and efficacy
  - Approval processes
  - Substitution
- **While we anticipate resolution of some outstanding legal issues (i.e. Supreme Court hearing), will not resolve all litigation**
- **Must use every approval to increase awareness and true comprehension of the biosimilar paradigm**
- The development pipeline does not stop. Biosimilars will have to be compared against not just their originator counterparts, but also new molecules that are continuing to be brought to market.
**Recommended Articles**


This reference offers a concise and thorough overview of how the principles of biosimilarity are built upon the foundation of comparability determination of originator biologics. This document also provides an insightful lens to help us establish an appropriate level of expectation for clinical data in biosimilars.


This excellent article frames the key areas of concern expressed by physicians during the introduction of biosimilars in Europe and provides scientifically justified explanations as to why biosimilars can be considered equally safe and effective to their originator counterparts.


This document is a great reference for helping end users the concept of extrapolation of indications for biosimilars.


This very good primer gives readers an introduction to the tests and techniques that support the analytical assessment of biosimilars.

**Links to Food and Drug Administration Advisory Committee Hearings on Biosimilars (as of April 8, 2017)**

FIlgrastim-sndz (Zarxio)
[https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm426351.htm](https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm426351.htm)

Infliximab-dyyb (Inflectra), Adalimumab-atto (Amjevita), Etanercept-szzs (Erelzi)
[https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm481975.htm](https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm481975.htm)
Link to Food and Drug Administration Guidances on Biosimilars

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm
